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APPLICATION NO	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO	CONFIRMATION NO
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EXAMINER	
DAVIS, MINH TAM B	

ART UNIT	PAPER NUMBER
1642	20

DATE MAILED: 06/04/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/341,829	LETHE ET AL.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 April 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,17-22,24,26,29,33,38,43,45,47,49 and 53-60* is/are pending in the application.

4a) Of the above claim(s) *4,5,20-22,24,26,29,33,43,45,47,49,54-56 and 60* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,6,7,17-19,38,53 and 57-59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Applicant cancels claim 61.

Accordingly, claims 1-3, 6-7, 17-19, 38, 53, 57-59 are examined in the instant application.

This application contains claims drawn to an invention nonelected with traverse in Paper No.8. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

The following are the remaining rejections.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, WRITTEN DESCRIPTION

1. Claims 1, 7, 17-19, 38, 53, 57-59 remain rejected under 35 USC 112, first paragraph, pertaining to lack of clear written description for reasons already of record in paper NO: 18.

Applicant argues that sequences that share enough sequence with SEQ ID NO:4 to hybridize under stringent conditions should by definition be considered a related sequence, not an unrelated sequence.

Applicant further asserts that this notion of related sequences is shown in Example 2, in which to screen for full length clones of LAGE-1 gene from a cDNA library of 75,000 clones, using a 137 bp probe, only 25 colonies hybridize to the LAGE-1 probe, even under reduced stringent conditions of 0.4X SSC at 63 C. Applicant asserts

that this represent only 0.03% of the total number of colonies screened. Applicant further asserts that the same principle was demonstrated in Example 4 for RNA using Northern blot. Applicant concludes that thus the sequences embraced by the rejected claims only represent related sequences, and not a vast genus of unrelated sequences as alleged by the Examiner.

Concerning complement in claim 7, Applicant argues that since the unique fragment has to be 15 nucleotide in length, the complement thereof would be at least 15 nucleotide in length. Applicant further argues that Applicant does not understand how a "complement" can be only partially complementary, since the standard notion of a complement of a nucleic acid molecule is a second antiparallel nucleic acid molecule in which the sequence is complementary so that the double helix can be formed. Applicant asserts that for every "A" in the first nucleic acid molecule, the complementary second nucleic acid molecule would have a "T", for every "C" in the first nucleic acid molecule, the complementary second nucleic acid molecule would have a "G", and so on.

Concerning unique fragment, Applicant argues that 1) the structural information is quite clearly provided by the sequence of SEQ ID NO:4 itself, and 2) excluding SEQ ID NO:8 was not intended, nor is it necessary, to provide structural information.

Applicant's arguments in paper No:19 have been considered but are found not to be persuasive for the following reasons:

It is noted that the sequences that hybridize to SEQ ID NO:4 are not limited to those that hybridize to the fragment of 137 bp used in Example 2, nor to a fragment of SEQ ID NO:4 of that size. Further the hybridizing sequences could be fragments, and

are not limited to full length sequences, or the sequences of the sizes of the clones in the screened library.

Thus contrary to Applicant's assertion, the hybridizing sequences encompass numerous unrelated sequences the complete structure nor function of which are not disclosed in the specification.

Further, one cannot determine that those 0.03% or 25 colonies that hybridize to the claimed probe of 137 bp would be related to or similar to SEQ ID NO:4, because based on sequence similarity one cannot predict the function of a protein, which could be completely different from that of SEQ ID NO:4. Bowie et al (Science, 1990, 257 : 1306-1310) teach that an amino acid sequence encodes a message that determine the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instruction of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex (col.1, p.1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitution can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col.2, p.1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess et al (J of Cell

Biol. 111:2129-2138, 1990) who teach that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein and by Lazar et al (Molecular and Cellular Biology, 1988, 8:1247-1252) who teach that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. These references demonstrate that even a single amino acid substitution will often dramatically affect the biological activity and characteristics of a protein. In addition, Bork (Genome Research, 2000,10:398-400) clearly teaches the pitfalls associated with comparative sequence analysis for predicting protein function because of the known error margins for high-throughput computational methods. Bork specifically teaches that computational sequence analysis is far from perfect, despite the fact that sequencing itself is highly automated and accurate (p. 398, col 1). One of the reasons for the inaccuracy is that the quality of data in public sequence databases is still insufficient. This is particularly true for data on protein function. Protein function is context dependent, and both molecular and cellular aspects have to be considered (p. 398, col 2). Conclusions from the comparison analysis are often stretched with regard to protein products (p. 398, col 3). Furthermore, recent studies show that alternative splicing might affect more than 30% of human genes and the number of known post-translational modifications of gene products is increasing constantly so that complexity at protein level is enormous. Each of these modifications may change the function of respective gene products drastically

(p. 399, col 1). Further, although gene annotation via sequence database searches is already a routine job, even here the error rate is considerable (p. 399, col 2). Most features predicted with an accuracy of greater than 70% are of structural nature and at best only indirectly imply a certain functionality (see legend for table 1, page 399). As more sequences are added and as errors accumulate and propagate it becomes more difficult to infer correct function from the many possibilities revealed by database search (p. 399para bridging cols 2 and 3). The reference finally cautions that although the current methods seem to capture important features and explain general trends, 30% of those feature are missing or predicted wrongly. This has to be kept in mind when processing the results further (p. 400, para bridging cols 1 and 2). Further, Scott et al (Nature Genetics, 1999, 21:440-443) teach that the gene causing Pendred syndrome encodes a putative transmembrane protein designated pendrin. Based on sequence similarity data, the authors postulated that the putative protein was deemed to be a member of sulfate transport proteins that included a 29% identity to rat sulfate-anion transporter, 32% similarity to human diastrophic dysplasia sulfate transporter, and 45% similarity to the human sulfate transporter downregulated in adenoma . However, upon analyzing the expression and kinetics of the protein, the data revealed no evidence of sulfate transport wherein results revealed that pendrin functioned as a transporter of chloride and iodide. Scott et al. suggest that these results underscore the importance of confirming the function of newly identified gene products even when the database searches reveal significant homology to proteins of known function (page 411, 1st column, 4th paragraph).

Clearly, given not only the teachings of Bowie et al, Scott et al, Lazar et al and Burgess et al but also the limitations and pitfalls of using computational sequence analysis and the unknown effects of alternative splicing, post translational modification and cellular context on protein function as taught by Bork, the function of those 0.03% or 25 colonies that hybridize to the claimed probe of 137 bp could not be predicted, based on sequence similarity with SEQ ID NO:4, nor would it be expected to be the same as that of SEQ ID NO:4.

Concerning complement in claim 7, although the unique fragment has to be 15 nucleotide in length, the complement thereof does not have to have at least 15 nucleotide in length, because a partial complement does not have to be complementary to the full length of the unique fragment. Although a complement of a nucleic acid molecule is a second antiparallel nucleic acid molecule in which the sequence is complementary, said complement does not have to be be complementary to the full length of the nucleic acid molecule.

Further, it is noted that the Examiner did not state that a "complement" can be only partially complementary. The Examiner stated that complements could be partial or full complement, wherein a partial complement could share with the claimed sequence only a fragment.

Concerning the claimed unique fragment of SEQ ID NO:4, although the full length sequence of SEQ ID NO:4 is disclosed, no disclosure is found concerning the structure of said unique fragment.

It is noted that nucleic acid sequences comprising a fragment of SEQ ID NO:4 remain rejected as well, since they encompass unrelated sequences that share a fragment with SEQ ID NO:4.

It is further noted that "an agent" that hybridizes under the stringent conditions as amended in claim 38 still encompasses nucleotide fragments with undisclosed structure and length that hybridize to SEQ ID NO:4 under the stringent conditions recited in claim 38.

2. Claim 6 remains rejected under 35 USC 112, first paragraph, pertaining to lack of clear written description of the claimed allelic variants for reasons already of record in paper NO: 18.

Applicant argues that Applicant is not claiming any possible allelic variant of SEQ ID NO:4, Applicant only claim those allelic variants that meet the element of claim 1. Applicant asserts thus Applicant has provided a written description of allelic variants of SEQ ID NO:4, because one would understand that Applicant provide sufficient information to be in possession of the claimed invention.

Applicant's arguments in paper No:19 have been considered but are found not to be persuasive for the following reasons:

Concerning the claimed allelic variants of claim 6, that hybridize to SEQ ID NO:4 under the stringent conditions recited in claim 1, the same reasons of rejection set forth above for sequences that hybridize to SEQ ID NO:4 under the stringent conditions recited in claim 1 apply here as well.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, ENABLEMENT

1. Claim 53 remain rejected under 35 USC 112, first paragraph, pertaining to lack of enablement for a composition that induces an immune response, for reasons already of record in paper NO: 18.

Applicant asserts the term vaccine has been removed and that one is enabled to make and use the claimed invention without exercising any other than routine experimentation, since measuring an immune response is well known in the art.

Applicant's arguments in paper No:19 have been considered but are found not to be persuasive for the following reasons:

As written, the claim 53 encompasses a composition comprising a nucleic acid composition encoding LAGE-1 or an immunogenic fragment thereof , wherein said nucleic acid could induce an immune response in a patient burdened with cancer.

It is however unpredictable that an immune response could be elicited by the claimed nucleic acid in a patient burdened with cancer, because immune suppression in cancer patients is well known in the art, and as taught by Boon, of record. Boon teaches that for active immunization in human patients we have to stimulate immune defenses of organisms that have often carried a large tumor burden. Establishment of immune tolerance may therefore have occurred and it may prevent immunization and several lines of evidence suggest that large tumor burdens can tolerize or at least depress the capability to respond against the tumor (p. 206, para 2).

Further, the claim 53 encompasses a nucleic acid composition for use in gene therapy to elicit an immune response in a patient with cancer. The state of the art at the

time of filing was that the combination of vector, promoter, protein, cell, target tissue, level of expression and route of administration required to target the tissue of interest and obtain a therapeutic effect using gene therapy, however, was unpredictable. For example, Miller (1995, FASEB J., Vol. 9, pages 190-199) review the types of vectors available for *in vivo* gene therapy, and conclude that "for the long-term success as well as the widespread applicability of human gene therapy, there will have to be advances...targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (page 198, column 1). Deonarain (1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69) indicate that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Deonarain reviews new techniques under experimentation in the art which show promise but states that such techniques are even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion section). Verma (Sept. 1997, Nature, Vol. 389, pages 239-242) reviews vectors known in the art for use in gene therapy and discusses problems associated with each type of vector. The teachings of Verma indicate a resolution to vector targeting has not been achieved in the art (see entire article). Verma also teaches appropriate regulatory elements may improve expression, but it is unpredictable what tissues such regulatory elements target (page 240, sentence bridging columns 2 and 3). Crystal (1995, Science, Vol. 270, page 404-410) also reviews various vectors known in the art and indicates that "among the design

hurdles for all vectors are the need to increase the efficiency of gene transfer, to increase target specificity and to enable the transferred gene to be regulated" (page 409).

2. Claims 58-59 remain rejected under 35 USC 112, first paragraph, pertaining to lack of enablement for a method for diagnosing cancer, using "an agent" in PCR, i.e. a single primer, for reasons already of record in paper NO: 18.

Applicant argues that the patent language such as "a", "an" and "the" is taken to mean one or more", and that in the instant claims, the term "the agent" means one or more agents. Applicant asserts that there are many examples in the literature of single primer PCR.

Applicant's arguments in paper No:19 have been considered but are found not to be persuasive for the following reasons:

The claims encompass a method for detecting cancer, using a single primer for PCR.

It is noted that Applicant assertion that there are many examples in the literature of single primer PCR is not supported by any reference. As taught by Sambrook et al, of record, two primers however are conventionally required for PCR. Further, the specification, nor the art at the time the invention disclose how to perform PCR using a single primer to detect SEQ ID NO:4 for diagnosing cancer.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, SCOPE

1. Claims 1, 7, 17-19, 38, 53, 57-59 remain rejected under 35 USC 112, first paragraph, pertaining to lack of enablement for a nucleic acid molecule that hybridizes under high stringent conditions as specified in claim 1 or 38 to SEQ ID NO:4, or complements thereof or complements of unique fragments thereof, or a method for diagnosing cancer using an agent that hybridizes under high stringent conditions recited in claim 38, for reasons already of record in paper NO: 18.

The same arguments and reasons for rejection under 112, first paragraph, written description apply here as well.

2. Claims 1, 6 remain rejected under 35 USC 112, first paragraph, pertaining to lack of enablement for allelic variants of SEQ ID NO:4, for reasons already of record in paper NO: 18.

Applicant asserts that the Examiner has not provided support for the contention that the principles of protein chemistry apply equally to nucleic acid chemistry. Applicant further asserts that the Examiner has not provided sound basis for applying the principles of protein chemistry, whatever the unpredictability of those principles may be, to the instant claimed invention.

Applicant's arguments in paper No:19 have been considered but are found not to be persuasive for the following reasons:

It is noted that substitution or deletion by nature of one or more nucleotides of a nucleic acid sequence would be translated into substitution or deletion one or more corresponding amino acids of the encoded polypeptide, wherein the effect of said substitution or deletion on function of the nucleic acid and the encoded polypeptide is

unpredictable, as taught by Burgess et al, Lazar et al, Tao et al, and Gillies et al, all of record.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 703-305-2008. The examiner can normally be reached on 9:30AM-4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, ANTHONY CAPUTA can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-

872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0916.

MINH TAM DAVIS

May 30, 2003

SUSAN UNGAR, PH.D
PRIMARY EXAMINER